REMARKS

I. Status of the Claims

Claims 1-3, 5-9 and 11-15 are being prosecuted.

Claim 13 is amended.

Claims 4, 10 and 24 are cancelled.

Claims 18-23 and 25-37 are withdrawn.

By this amendment, claim 13 has been modified to correct a spelling error and a punctuation error.

II. The Remaining Bar to Patentability is Obviousness

Claims 1-3, 5-9 and 11-15 were rejected under 35 U.S.C. §103(a) as obvious over the combined teachings of Kröger et al. *General Pharmacology*, Vol. 28, No. 2 pp. 257-263, 1997) in view of Ogata et al. (U.S. Patent No. 5,478,815) and Murdock et al. (U.S. Patent NO. 4,526,788). Applicant respectfully traverses the rejection.

The Kröger et al. 1997 reference entitled "Protection from Acetaminophen - induced liver damage by the synergistic action of low doses...of nicotinamide and ...N-acetylcystine or ...L-methionine" relates an attempt to mitigate acetaminophen hepatotoxicity but uses intraperitoneal administration in animals, not a method generally used in humans, and doses that translate to higher non-IP doses in humans, than in the present claims. The end point is release of GOT and GPT.

Independent claims 1 and 13 relate a composition of a hepatotoxic compound with methionine and nicotinamide. The claim elements as amended are not taught or suggested by a publication which teaches ameliorating hepatoxicity, when the authors of the further work (Kröger et al., 1999) of the cited publication demonstrate that nicotinamide at certain doses is ineffective and even counterproductive.

Applicant has previously stated on the record that the Kröger et al. 1999 publication cited by the European examiner in a related case (see Supplemental IDS filed October 20, 2008) taught away from the present invention. The argument was presented on page 8, second paragraph of the Amendment mailed on April 9, 2009. However, the Examiner neither refuted nor responded to this point in the final Office Action mailed August 6, 2009.

Since the Examiner may not have considered this point, Applicant would like to again emphasize that in Table 5, page 205 of the H. Kröger et al. *General Pharmacology* 33:203-

206, 1999 publication, it is demonstrated that administering 50 mg/kg of nicotinamide intraperitoneally to mice along with 50 mg/kg methotrexate and 50 mg/kg acetaminophen produced (increased) liver toxicity as shown by significantly higher GOT and GPT elevations, compared to mice receiving 50 mg/kg methotrexate plus 50 mg/kg acetaminophen alone, noting that elevated GOT and GPT are indicators of liver damage. Additionally, Table 5 demonstrates that higher doses of nicotinamide, nonetheless provided no protection against combined methotrexate/acetaminophen-induced liver toxicity. Consequently, Kröger teaches that **nicotinamide is non-hepatoprotective** at high nicotinamide dosages, and at lower nicotinamide dosages, **nicotinamide increases liver damage** from methotrexate and acetaminophen.

The data in the Kröger et al 1999 reference teaches the direct opposite of the present application regarding nicotinamide's protective effects. It is applicant's position that those of skill in the art would not be guided to the present invention after consultation of the single Kröger 1997 reference in the abstract without considering the body of Kröger work, including the 1999 findings, if they were trying to develop a composition that includes a hepatotoxic compound but mitigates its adverse effects.

The deficiencies of the Kröger et al 1997 publication are not cured by the Ogata et al. and Murdock et al. publications, as the Examiner stated that these references have been cited to demonstrate: 1) routine knowledge of using intraperitoneal (IP) injection as experimental animal testing; and 2) to demonstrate routine knowledge in calculating human dosage based upon the interrelationship of dosages for animals of various sizes and species, and humans, respectively. Ogata et al. and Murdock et al. neither teach nor suggest the effective combination presently claimed. Therefore, Applicant continues to assert that the combined teachings of the cited publications do not render the aspects of the invention as set forth in independent claims 1 and 13, obvious. The more specific dependent claims are also not rendered obvious by the combined teachings of the cited reference for the same reason.

Moreover, Applicant notes that the examiner had found previously found claims 13-15 to be allowable in the Office Action dated February 28, 2008, although the indication of allowability was withdrawn in the Office Action dated December 19, 2009.

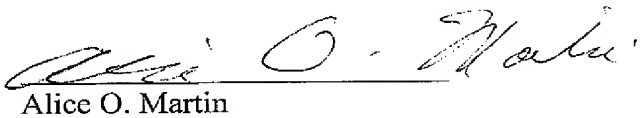
Applicant requests that the rejection under 35 U.S.C. §103(a) over Kröger et al. 1997, Ogata et al. and Murdock et al. be withdrawn.

III. Conclusion and Summary

For the reasons stated above, Applicant requests reconsideration, withdrawal of the outstanding rejections and allowance of the pending claims.

No fees are believed due at this time, however, please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (41959-102739).

Respectfully submitted,



Alice O. Martin
Registration No. 35,601
Attorney for Applicant

Date: September 4, 2009
Barnes & Thornburg LLP
P.O. Box 2786
Chicago, IL 60690-2786

CHDS01 AOM 555397v1